Remarks

Claims 13, 15-16, and 18-24 were pending; claims 16 and 24 are amended herein; claims 22-23 are canceled herein. As a result, claims 13, 15-16, 18-21, and 24 are pending.

The amended claims are supported throughout the originally filed specification and claims. Claim 16 is supported, e.g., by originally filed claims 16 and 17; at page 1, line 13; page 2, line 5 to page 3, line 7; page 4, lines 3-6; page 9, line 19 to page 10, line 6; and page 30, lines 3-4. Claim 24 is amended only in its dependency, and is supported, e.g., by originally filed claim 17.

Objection to the Specification

The Examiner required correction of the priority citation to Application No. 09/413,958 to cite the patent number of this application, which has now issued as a patent. The first paragraph of the specification is amended herein to update the priority data to cite the patent number.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph

Claims 16, 18, and 22-24 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method of screening for compounds that increase bone mineral density in vivo, wherein the loss of bone mineral density is the result of osteoporosis allegedly does not reasonably provide enablement for an in vitro method of screening for compounds that increase bone mineral density, nor a method for screening for increase in bone mineral density in any non-osteoporotic patient population or animal model. This rejection, insofar as it may apply to the amended claims, is respectfully traversed.

To facilitate prosecution, Applicants have amended claim 16 to recite

> A method of screening for compounds that increase bone mineral density, comprising the steps of:
>
> (a) contacting osteoblast and osteocyte cells in vivo with either a glucocorticoid or a test compound; and
>
> (b) comparing the number of said osteoblast and osteocyte cells undergoing apoptosis following treatment with said glucocorticoid to

> the number of said osteoblast and osteocyte cells undergoing apoptosis following treatment with said test compound,
> wherein a lower number of apoptotic cells following treatment with said test compound than with said glucocorticoid is indicative of a compound that increases bone mineral density in osteoporotic patients.

Applicant believes that these amendments to recite contacting in vivo and to recite that the test result is indicative of a compound that increases bone mineral density in osteoporotic patients obviates the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Rejection of the Claims Under 35 U.S.C. §102

Claims 13, 15, 16, 18, 20, 21, 23, and 24 were rejected under 35 U.S.C. § 102(a) as being anticipated by Weinstein et al. (1998, *J. Clin. Invest.* 102:274-282). This rejection is respectfully traversed.

With this response Applicants are submitting a Katz Declaration under 37 C.F.R. § 1.132 (*In re Katz*, 687 F.2d 450, 215 U.S.P.Q. 14 (CCPA 1982); M.P.E.P. § 2132.01). In the Declaration, Drs. Manolagas, Jilka, and Weinstein declare:

> A. Michael Parfitt is a professor emeritus at the University of Arkansas for Medical Sciences. In the course of our conducting the research reported in the cited Weinstein et al. paper, he served as an advisor for us. He did not perform any of the experiments reported in the paper, and he did not conceive the hypothesis tested in the paper that glucocorticoid excess may affect the birth or death rate of bone cells, thus reducing their numbers.

They also declare that although Dr. Parfitt is a coauthor of the cited paper, he is not a coinventor of the subject matter disclosed therein (paragraph 4).

Under the rule of *In re Katz* and under M.P.E.P. 2132.01, this Declaration establishes that Mr. Parfitt is not an inventor and that the cited Weinstein et al. paper discloses the work of the Applicants. Since the cited Weinstein et al. paper discloses the work of the Applicants, it is not the work of "another" and is therefore not prior art under 35 U.S.C. § 102(a) (*In re Katz, supra*; M.P.E.P. § 2132.01).

In view of these remarks and the enclosed Katz Declaration under 37 C.F.R. § 1.132, Applicants respectfully request withdrawal of the rejection of claims 13, 15, 16,

18, 20, 21, 23, and 24 are under 35 U.S.C. § 102(a) as being anticipated by Weinstein et al. (1998, *J. Clin. Invest.* 102:274-282).

The Rejection of the Claims Under 35 U.S.C. §103

Claims 19 and 22 were rejected under 35 U.S.C. § 103(a) as being obvious over Weinstein et al. (1998, *J. Clin. Invest.* 102:274-282) as applied to claims 13, 15, 6, and 18 in view of Jilka et al. (1997, *J. Bone and Mineral Res.* 12 (supplement): S455, abstract S411) and Kato et al. (1997, *J. Bone and Mineral Res.* 12:2014-2023). This rejection is respectfully traversed.

Weinstein et al. is removed as prior art by the enclosed Katz Declaration under 37 C.F.R. 1.132 by the co-inventors Drs. Manolagas, Jilka, and Weinstein, as is discussed above.

Jilka et al. discloses investigating the effect of glucocorticoids and the IL-6 cytokine on apoptosis in primary cultures of bone marrow cells stimulated to differentiate into osteoblasts. Jilka et al. reports contacting bone marrow cells with dexamethasone beginning after 6 days of culture. The abstract discloses that bone marrow cell cultures contacted with dexamethasone produced more apoptotic cells than untreated control cultures after 10 days of culture and after 20-30 days of culture. Jilka et al. discloses that if IL-6 was added to the cultures 24 hours before dexamethasone was added, it decreased dexamethasone-induced apoptosis. Jilka et al. discloses that in the 20-30 day cultures, some of the apoptotic cells had characteristics suggesting they were osteoblasts.

Kato et al. (1997, *J. Bone Mineral Res.* 12:2014-2023) discloses the establishment of an osteocyte-like cell line, MLO-Y4 (abstract).

Three criteria must be met in order to establish a *prima facie* case of obviousness. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation in the references or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine reference teachings to arrive at the claimed invention. Third, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. M.P.E.P. § 2142.

The pending claims recite contacting osteoblast and osteocyte cells with either a glucocorticoid or a test compound. Applicants discovered that the increase in apoptosis with glucocorticoid treatment was more dramatic in osteocytes than osteoblasts. The percentage of osteoblasts undergoing apoptosis increased 3-fold in mice treated with prednisolone (page 28, lines 17-19), whereas the percentage of osteocytes undergoing apoptosis increased by an infinite factor, going from none in the controls to 28% in the prednisolone-treated mice (page 29, lines 8-10). In contrast, Jilka et al. discloses only contacting bone marrow containing osteoblast progenitor cells with a glucocorticoid. Osteocytes are not disclosed to be present. Therefore, Jilka et al. does not disclose all of the elements of any of the present claims.

In addition, Jilka et al. discloses contacting the bone marrow osteoblast progenitor cells with a glucocorticoid (dexamethasone), or with the glucorticoid plus IL-6. In contrast, the pending claims recite contacting the osteoblast and osteocyte cells with either a glucorticoid or a test compound.

Furthermore, the pending claims recite methods of screening for compounds that stimulate bone development or increase bone mineral density. The claims recite comparing the number of osteoblast and osteocyte cells undergoing apoptosis following treatment with a glucocorticoid to the number undergoing apoptosis following treatment with a test compound, wherein a lower number of apoptotic cells following treatment with said test compound than with said glucocorticoid is indicative of a compound that stimulates bone development (claims 13, 15, and 19-21) or indicative of a compound that increases bone mineral density (claims 16, 18, and 22-24). Jilka et al. does not disclose or suggest any screening program. It does not disclose that a lower number of apoptotic cells following treatment with a test compound than following treatment with a glucocorticoid is indicative of a compound that stimulates bone development or that it is indicative of a compound that increases bone mineral density.

For all the above reasons, Jilka et al. does not disclose all of the elements of any of the present claims. Kato does not fill in any of these deficiencies, since it is cited only for teaching the establishment of an osteocyte-like cell line. Weinstein et al. is removed as prior art by the enclosed Rule 132 Katz Declaration. Accordingly, the cited references, individually or cumulatively, do not teach or suggest all the elements of any

of the present claims. They also do not provide any suggestion or motivation to modify reference teachings to arrive at the presently claimed invention. They therefore fail to establish at least two of the three requirements for a *prima facie* case of obviousness. Therefore, Applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) over Weinstein et al. in further view of Jilka et al. and Kato et al.

Conclusion

Applicants believe that the claims are in condition for allowance. The Examiner is invited to telephone Applicant's attorney (651-207-8270) to facilitate prosecution of this application.

Respectfully submitted,

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Date 10/26/2006 By: Hugh McTavish

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient first class postage, in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this day of October 26, 2006.

Hugh McTavish